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Cytomegalovirus Glomerulopathy and Cytomegalovirus Interstitial Nephritis on Sequential Transplant Kidney Biopsies

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Abstract

Cytomegalovirus (CMV) nephropathy may be seen in kidney transplant biopsy specimens. We report a CMV-negative patient who received a kidney transplant from a CMV-positive donor and subsequently developed CMV glomerulopathy and CMV-associated interstitial nephritis, as observed in 2 sequential kidney biopsies. The first biopsy specimen showed CMV-positive endothelial cells in glomerular capillaries and CMV-infected monocytes in glomerular capillary lumens. The second biopsy specimen showed CMV-positive cells in the interstitium with associated lymphoplasmacytic infiltrate and tubular injury, but no evidence of direct CMV infection in tubular epithelial cells. Moreover, the second biopsy specimen showed persistent monocytes with cytoplasmic viral particles within glomerular capillary loops by electron microscopy. Our case shows that CMV glomerulopathy can be caused by direct CMV infection of glomerular capillary endothelial cells. CMV-positive circulating monocytes may play an important role in the different histopathologic manifestations of CMV nephropathy in kidney transplant grafts.

INDEX WORDS:

Transplant; cytomegalovirus (CMV) glomerulopathy; monocytes; tubular injury

INTRODUCTION

Cytomegalovirus (CMV) infection is a well-documented complication in kidney transplant recipients, especially when a seronegative recipient receives a transplant from a seropositive donor.^{1,2} CMV glomerulopathy, with or without tubulointerstitial involvement, has been reported previously and may occur despite prophylactic therapy.^{3–7} Transplant kidneys with CMV glomerulopathy often lack significant inflammatory infiltrate in glomeruli and direct evidence of glomerular cell infection by CMV, an observation that has led some authors to question the mechanisms and significance of CMV-mediated glomerular injury.⁸ We present 2 sequential transplant kidney biopsies that revealed different histopathologic manifestations

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of CMV infection. The specimen from the first kidney biopsy showed CMV glomerulopathy with CMV-positive endothelial cells and CMV-positive monocytes in glomerular capillaries. A specimen from a subsequent kidney transplant biopsy showed interstitial nephritis with CMV-positive interstitial cells, but absence of CMV virus in tubular epithelial cells and glomerular endothelial cells.

Our teaching case shows that CMV glomerulopathy is associated with direct CMV infection of glomerular endothelial cells. Moreover, CMV interstitial nephritis can be seen without overt tubular epithelial cell infection. As our case shows, both lesions can occur in the same kidney transplant at different times in the posttransplantation course. Both biopsy specimens showed circulating monocytes with cytoplasmic CMV particles in the lumen of glomerular capillaries. The presence of circulating CMV-infected monocytes in both biopsy specimens and their association with different histopathologic lesions may indicate that virus-carrying monocytes may play an important role in persistent CMV infection of a kidney transplant.

CASE REPORT

Clinical History and Initial Laboratory Data

A 48-year-old man was seen in the transplantation clinic for evaluation of an increase in serum creatinine level approximately 12 weeks after deceased donor kidney transplantation. Up until a week prior to evaluation, his serum creatinine level had been decreasing slowly to a nadir of 1.6 mg/dL (corresponding to estimated glomerular filtration rate [eGFR] of 60 mL/min/1.73 m², as calculated with the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] cystatin C equation).⁹ His posttransplantation course had been complicated by delayed transplant function attributed to prolonged warm ischemia time requiring 5 doses of thymoglobulin and 3 hemodialysis treatments for hyperkalemia. A biopsy at that time was notable for acute tubular injury without evidence of acute cellular rejection or viral infection.

The patient's medical history was significant for end-stage renal disease secondary to hypertension and diabetes mellitus. His pretransplantation evaluation was negative for Epstein-Barr virus, CMV, and polyoma virus. He received a kidney from a CMV-positive, Epstein-Barr virus–positive donor who had died after head trauma from a motor vehicle accident. The donor did not meet expanded-criteria donor or donation after cardiac death criteria, and the duration of cardiac arrest/downtime was 25 minutes.

Approximately 4 weeks after transplantation, the patient began reporting soft stools in the absence of fevers or abdominal pain. Because CMV serologic test results were indeterminate at that time, the soft stools were attributed to mycophenolate mofetil and dosing was decreased from 1,500 mg to 500 mg twice daily. During this time, prophylactic valganciclovir, which had been dosed at 450 mg every other day, was increased to 450 mg daily as his eGFR began to improve. Quantification of CMV in plasma by polymerase chain reaction (PCR) showed 3,679,370 copies/mL. He was admitted for 2 days of intravenous ganciclovir treatment and transitioned to oral valganciclovir, 900 mg, orally twice daily for discharge.

Upon returning to the transplantation clinic 1 week later, the patient's physical examination showed blood pressure of 118/70 mm Hg, heart rate of 102 beats/min, and weight of 106.0 kg. He had clear lungs, unremarkable abdominal examination findings, and no edema. Urinalysis detected protein (1+) without red blood cells or casts. Creatinine level was 2.4 mg/dL (eGFR, 31 mL/min/1.73 m²). Serum albumin level was 4.0 g/dL. PCR quantification of CMV in serum detected 3,501,130 copies/mL. Unfortunately, urine protein quantification and urinalysis were not ordered. A kidney biopsy was performed.

Kidney Biopsy 1

Light microscopy showed 14 glomeruli, none of which was sclerosed. There was mild interstitial edema, but no interstitial inflammatory infiltrate. Glomeruli showed endothelial cells with enlarged nuclei, nuclear inclusions, and smudgy chromatin. Several capillaries showed monocytes with enlarged nuclei, smudgy chromatin, and cytoplasmic CMV-type inclusions (Fig 1A). An anti-CMV immunohistochemistry stain was positive in glomerular endothelial cells and intracapillary monocytes (Fig 1A). There was no evidence of simian virus 40 (SV40) antigens by immunohistochemistry. Vessels did not show significant abnormalities. Immunofluorescence studies did not show evidence of immune complex deposits. Electron microscopy examination showed CMV-type viral inclusions, some with targetoid features, in the cytoplasm of endothelial cells of the glomerular tuft and the cytoplasm of monocytes (Fig 1B and C). The cytoplasmic viral particles varied in size from 125–250 nm, which is consistent with the size range described for CMV particles (Fig 1D).¹⁰ CMV dense core particles were seen in the nuclei and cytoplasm of monocytes (Fig 1C and D). No immune complex deposits were identified by electron microscopy. The tubular epithelium showed loss of brush border. No viral particles were identified in tubular epithelial cells.

Diagnosis 1

CMV glomerulopathy and acute tubular injury.

Clinical Follow-up 1

CMV titers were measured approximately 6 weeks after this biopsy but showed no improvement despite valganciclovir treatment, with serum CMV quantification by PCR of 45,569,300 copies/mL. Mycophenolate mofetil therapy was discontinued, but the patient was continued on treatment with prednisone, 5 mg, daily and tacrolimus, 10 mg, orally twice daily. CMV genotyping was performed, showing mutations of the leucine at amino acid 595 of the viral UL97 protein to tryptophan and serine (UL97:L595W and UL97:L595S), consistent with strains resistant to ganciclovir and susceptible to foscarnet and cidofovir. After consultation with the infectious disease section, foscarnet, 5,000 mg, intravenously daily, was started, with a plan to transition to cidofovir if there was no response. Over the next 2 months on foscarnet, his viral titer never trended to <10,000 copies/mL, and his baseline creatinine level remained in the 2.6- to 3.2-mg/dL range (eGFR, 22–28 mL/min/1.73 m²). Serum albumin level was 3.6 mg/dL. In the third month of therapy, he began experiencing symptoms of nausea and vomiting and underwent upper endoscopy with a biopsy of the pylorus. He was found to have 2 endothelial cells with ill-defined eosinophilic inclusion that stained positively with CMV immunostain. Foscarnet therapy was

discontinued and he was started on treatment with cidofovir. Two weeks after initiation of cidofovir therapy, his creatinine level increased to 6.3 mg/dL (eGFR, 10 mL/min/1.73 m²). A second kidney biopsy was performed.

Kidney Biopsy 2

This kidney biopsy specimen showed 19 glomeruli, none of which was globally sclerosed. There was interstitial fibrosis involving 20%–25% of the biopsied tissue. There were focal areas of lymphocytic infiltrate with a prominent plasma cell component. Tubules were diffusely dilated and showed flattened epithelium with enlarged reactive nuclei. Glomeruli showed an increase in mesangial cellularity, but there were no endothelial cells with enlarged nuclei or cytoplasmic inclusions. The interstitium showed several cells with enlarged nuclei with inclusions, and some with cytoplasmic inclusions (Fig 2A and B). Anti-CMV immunohistochemistry stain showed positive cells in the interstitium, but absence of CMV-positive cells in glomeruli or tubules (Fig 2C). SV40 was undetectable by immunohistochemistry. Ultrastructural examination showed glomeruli with patent capillary lumens. There was mild thickening and mild corrugation of glomerular basement membranes. Podocytes showed diffuse foot-process effacement. No electron-dense immune complex deposits were identified. CMV viral particles were identified in occasional circulating monocytes within capillary lumens (Fig 2D).

Diagnosis Biopsy 2

Severe acute tubular injury with CMV-associated interstitial nephritis.

Clinical Follow-up 2

After the second biopsy, the patient was started on treatment with CMV immunoglobulin (Cytogam) in addition to cidofovir. His creatinine level did not improve, remaining 6.3 mg/dL (eGFR, 10 mL/min/1.73 m²). His CMV titers remained high at 630,737 copies/mL. Subsequently, he had one episode of a sudden increase in serum creatinine level to 7.6 mg/dL, attributed to volume losses from chlorthalidone use. However, his creatinine level returned to 6.3 mg/dL. The patient was restarted on CMV immunoglobulin (Cytogam) without improvement. Approximately 8 months after transplantation, he was started on hemodialysis therapy because there was no expectation of kidney recovery.

DISCUSSION

CMV nephropathy may manifest in kidney transplant recipients with various histopathologic lesions (Table 1) despite prophylactic antiviral therapy.^{7,11} CMV nephropathy often is characterized by a tubulointerstitial nephritis with nuclear and cytoplasmic inclusions in the tubules.¹² Less common is isolated glomerulopathy of the CMV-infected transplant.⁶ The underlying pathophysiologic mechanisms leading to the different histopathologic manifestations of CMV nephritis are still enigmatic. Electron microscopic, immunohistochemical, or in situ hybridization studies are required to support the biopsy diagnosis of CMV-induced glomerulopathy.^{13,14}

Richardson et al³ first reported CMV nephropathy with predominant glomerular involvement in 14 kidney transplant recipients. Glomerular findings in those transplant biopsy specimens were variable; the majority showed endothelial cell hypertrophy, necrosis, and mononuclear cell infiltrate, but no evidence of CMV inclusions by electron microscopy.³ Several authors therefore proposed that the glomerular lesions associated with CMV infection could represent a form of T-cell-mediated transplant rejection, even in the absence of CMV in glomeruli.^{5,15} This conclusion was based on the presence of intraglomerular CD8⁺ T lymphocytes and expression of HLA class II antigens in mononuclear cells.^{15,16} However, Herrera et al⁸ reported several cases with similar glomerulopathy in CMV-positive transplant recipients without evidence of glomerular T-cell infiltrates or presence of virus in glomeruli by immunofluorescence microscopy or electron microscopy. These authors concluded that glomerular lesions in the setting of a CMV-positive transplant recipient resulted from anti-endothelial antibody-mediated injury.⁸ Rarely, CMV infection may induce de novo glomerulonephritis.¹⁷

CMV glomerulopathy usually is not associated with an interstitial inflammatory infiltrate.^{6,18,19} Whereas the first biopsy specimen of our patient showed CMV glomerulopathy without interstitial nephritis, the second biopsy specimen showed CMV-positive cells only in the interstitium without CMV glomerulopathy. Viral inclusions in glomerular endothelial cells and monocytes were confirmed by immunoperoxidase stain in the first biopsy specimen, indicating that both direct infection of glomerular cells and infected monocytes may play a role in CMV glomerulopathy. In the second biopsy specimen, we identified CMV-positive cells in only the interstitium and circulating monocytes, confirming the previous observation that CMV-associated interstitial nephritis often lacks evidence of CMV-positive tubular epithelial cells.⁶ Our findings, together with those reported in the literature, raise the question of separate pathologic mechanisms involved in CMV glomerulopathy. One is through direct infection of glomerular cells by CMV, while additional mechanisms may include antibody-mediated⁸ or cytokine-mediated¹⁹ injury. Monocytes carrying CMV virus may play an important role in these later pathologic mechanisms by releasing cytokines that induce both tubular and glomerular injury.²⁰

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Figure 1.

First kidney biopsy. (A, B): Glomeruli show capillary endothelial cells with nuclear positivity for cytomegalovirus (CMV) by immunohistochemistry (A: arrows; peroxidase-conjugated anti-CMV antibody; original magnification, $\times 400$) and cytoplasmic CMV viral particles by electron microscopy (B: arrow; original magnification, $\times 14,000$). CMV-positive monocytes in capillary loops showed positive nuclear and cytoplasmic staining (A: star). (C) Electron microscopic examination shows an intracapillary monocyte with nuclear CMV inclusions (star) and cytoplasmic CMV virus particles (arrow; original magnification, $\times 12,000$). (D) Ultrastructural measurements of the cytoplasmic viral particles show a large variation in size ranging from 125–250 nm in diameter (arrow; original magnification, $\times 14,000$).

Figure 2. Second kidney biopsy. (A, B) Diffuse severe tubular injury with occasional interstitial cells with enlarged nuclei and cytoplasmic inclusions (arrows; hematoxylin and eosin; original magnification, $\times 400$). There is focal lymphocytic and plasmacytic interstitial infiltrate with edema. (C) Immunohistochemistry shows staining of cytomegalovirus (CMV)-positive cells in the interstitium (arrow; peroxidase-conjugated anti-CMV antibody; original magnification, $\times 400$). Glomeruli show mild mesangial hypercellularity but no CMV-positive endothelial cells. (D) Occasional monocytes with cytoplasmic virus particles (arrow) were still found within some capillary lumen of the glomeruli (original magnification, $\times 12,000$).

Table 1.**CMV Nephropathy Histology**

Lesion		Morphology	Reference
CMV glomerulopathy	Endothelial swelling, mononuclear cell infiltrate, foot-process effacement, with or without CMV positive IHC		3, 5, 6
CMV interstitial nephritis	Interstitial mononuclear infiltrate, enlarged tubular epithelial cells, with or without CMV inclusions		4, 12
CMV-associated GN	Immunotactoid glomerulopathy		4, 17

Abbreviations: CMV, cytomegalovirus; GN, glomerulonephritis; IHC, immunohistochemistry.